08.08.03

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Stephen Hordley

Dated 22 July 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
L
10 AUG 2002
NEWPORT

The Patent Office

PCT/JP03/10119
12AUG02 E740167-1 D01030
P01/7700 0.00-0218630.2

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1.	Your Reference	**HQ/PG4924**
2.	Patent application number *(The Patent office will fill in this part)*	0218630.2
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**Tanabe Seiyaku Co. Ltd.** **2-10 Dosho-Machi 3-Chome** **Chuo-Ku,** **Osaka** **Japan**
	Patents ADP number *(if you know it)*	07493200001
	If the applicant is a corporate body, give the country/state of its corporation	**Japan**
4	Title of the invention	**NOVEL COMPOUNDS**
5	Name of your agent *(if you know one)*	**HELEN QUILLIN**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **CORPORATE INTELLECTUAL PROPERTY** **980 GREAT WEST ROAD** **BRENTFORD, MIDDLESEX** **TW8 9GS, GB**
	Patents ADP number *(if you know it)*	07057900 3

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Description	17
Claim(s)	4 DM
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. Helen Quillin

I/We request the grant of a patent on the basis of this application

Signature Dr Helen Quillin 9 August 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

LESLEY WELLS

01438 76 8599

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form

If you have answered "Yes" Patents Form 7/77 will need to be filed.

d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

PG4924

Novel Compounds

The present invention relates to novel compounds, processes for their preparation, compositions comprising them and their use in the treatment of diseases capable of being modulated by the inhibition of cell adhesion. More particularly the present invention related to novel heterocyclic compounds that inhibit α_4 integrin mediated cell adhesion and which are useful for the treatment of chronic inflammatory diseases.

The multiple adhesive interactions between leukocytes and endothelial cells or extracellular matrix proteins are a key factor in the regulation of immunity and inflammation. The earliest events in the migration of leukocytes out of the vasculature at site of inflammation include leukocyte rolling followed by changes in integrin avidity, which lead to subsequent firm adhesion (for reviews see Butcher, *Cell* 67:1033-1036 (1991); Harlan, *Blood* 3:513-525 (1985); Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Osborn, *Cell* 62:3-6 (1990); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); Springer, *Nature* 346:425-434 (1990); and Springer, *Cell* 76:301-314 (1994)). In response to chemotactic factors, the leukocytes migrate through two adjacent endothelial cells and into tissues that are composed, in part, of the extracellular matrix protein fibronectin (FN) (see Wayner et al., *J. Cell Biol.* 105:1873-1884 (1987)) and collagen (CN) (see Bornstein et al., *Ann. Rev. Biochem.* 49:957-1003 (1980); and Miller, Chemistry of the collagens and their distribution, in "Extracellular Matrix Biochemistry", K.A. Piez and A.H. Reddi, editors, Elsevier, Amsterdam, 41-78 (1983)). Important recognition molecules that participate in these adhesive reactions belong to the integrin gene superfamily (for reviews see Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Hynes, *Cell* 48:549-554 (1987); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); and Springer, *Nature* 346:425-434 (1990)).

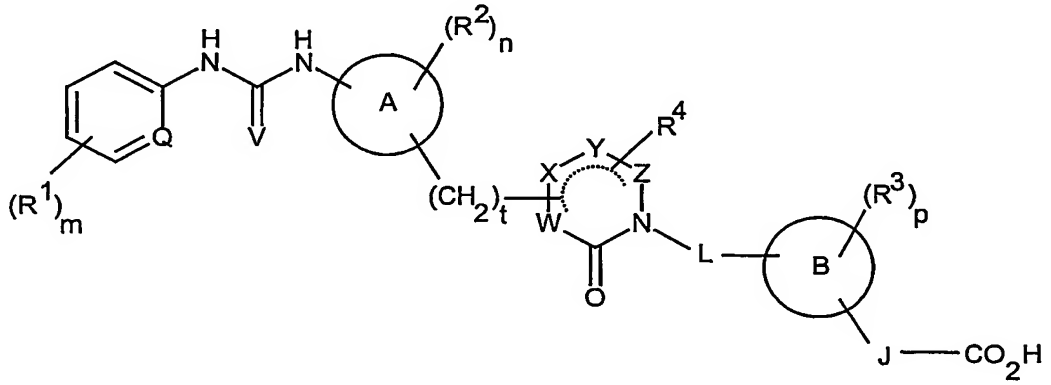
Integrins are heterodimers composed of non-covalently associated subunits, referred to as the alpha (α) and beta (β) subunits. To date, 8 integrin β subunits have been identified which can associate with 16 distinct α subunits to form 23 distinct integrins.

The $\alpha_4\beta_1$ integrin, also known as VLA-4 (Very Late Antigen-4), is constitutively expressed on the surface of leukocytes including lymphocytes,

monocytes, eosinophils and basophils (see Hemler et al., *J. Bio. Chem.* 262:11478-11485 (1987); and Bochner et al., *J. Exp. Med.* 173:1553-1556 (1991)). VLA-4 is reported to be present on neutrophils from septic patients (see Ibbotson et al., *Nature Med.* 7:465-470 (2001)). VLA-4 binds to vascular cell adhesion molecule-1 (VCAM-1) on activated endothelial cells, resulting in extravasation of leukocytes (Elices et al., *Cell* 60:577-584 (1990)). Once the cells have reached the extravascular space, VLA-4 can bind to the connecting segment 1 (CS-1), an alternatively spliced region of the FN A chain (Wayne et al., *J. Cell Biol.* 109:1321-1330 (1989)). In addition, VLA-4 is known to bind to osteopontin, a protein upregulated in arteriosclerotic plaques (see Bayless et al., *J. Cell Science* 111:1165-1174 (1998)).

Many classes of low molecular weight compounds that are claimed to inhibit α_4 integrin mediated cell adhesion are known in the art. For example, patent applications EP 1203766 and EP 1213288 describe a series of carboxylic acid derivatives that are claimed to inhibit the binding of $\alpha_4\beta_1$ integrin to its receptors, for example VCAM-1 and fibronectin.

A novel series of compounds has now been found which also inhibit α_4 integrin mediated cell adhesion. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



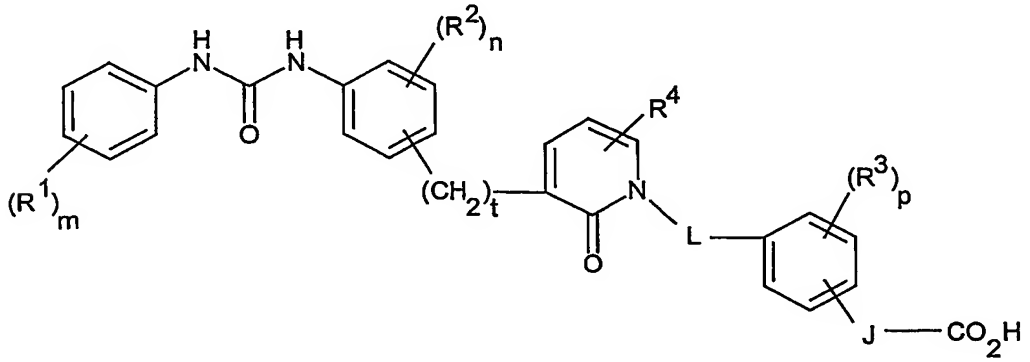
(I)

wherein

A and B are independently aryl or heteroaryl;

Q is C, CH or together with the group V forms a 5 or 6 membered heterocyclic ring;
R^1, R^2 and R^3 are independently C_{1-6}alkyl, halogen, C_{1-6}alkoxy, hydroxy, cyano, CF_3, nitro, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino, carboxy, C_{1-6}alkanoyl, amido, mono or di-C_{1-6}alkyl amido, $NHCOR^9$ or $NHSO_2R^9$ in which R^9 is C_{1-6}alkyl, C_{3-7}cycloalkyl or phenyl optionally substituted by up to three groups selected from C_{1-6}alkyl, halogen, C_{1-6}alkoxy, cyano, phenyl or CF_3;
R^4 is hydrogen, C_{1-6}alkyl, halogen or C_{1-6}alkoxy;
V is O, S, NH, N-C_{1-6}alkyl, NNO_2 or NCN or V together with the group Q forms a 5 or 6 membered heterocyclic ring;
W, X, Y and Z are independently C, CH or CH_2;
------ represents a single or double bond;
L is $-(CH_2)_q-$ where q is 0, 1, 2 or 3;
J is (i) a group $-CR^5=CR^6-$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl; or
(ii) a group $-CHR^7-CHR^8-$ where R^7 and R^8 are independently hydrogen, C_{1-6}alkyl or is a group $NHCOR^9$ or $NHSO_2R^9$ in which R^9 is as defined above.
m, n and p are independently 0, 1, 2 or 3;
t is 0, 1 or 2.

A particularly preferred sub-class of the compounds of formula (I) are the compounds of formula (Ia) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(Ia)

wherein:
R^1, R^2, R^3, R^4, L, J, m, n, p and t are as defined in formula (I).

Throughout the present specification the term 'halogen' is used to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine. Alkyl groups, whether alone or as part of another group, may be straight chain or branched. Preferred C_{1-6}alkyl groups include methyl, ethyl, n-propyl, n-butyl, isopropyl and tert-butyl.

The term "aryl" is used to denote phenyl and naphthyl . The term naphthyl is intended to include both naphth-1-yl and naphth-2-yl groups.

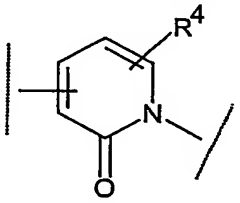
The term "heteroaryl" is intended to mean an aromatic or a benzofused aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such benzofused aromatic rings include quinolinyl, isoquinolinyl, indolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl and the like. The heteroaryl ring, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Within the definition of the compounds of formula (I)

It will be appreciated that Q can be C not only when forming a 5 or 6 membered heterocyclic ring but also when substituted by an R^1 group.

When A and/or B is aryl a preferred group is phenyl.

When m, n or p is other than 0, preferred R^1, R^2 and R^3 groups respectively include C_{1-6}alkyl, halogen, C_{1-6}alkoxy, cyano or CF_3. When m, n or p is 2 or 3 the groups R^1, R^2 and R^3 respectively can be the same or different.

Preferably the ring containing W, X, Y and Z is 

When Q and V combine together to form a 5 or 6 membered heterocyclic ring, suitable examples are those in which Q and V form part of a benzimidazole or benzoxazole ring.

Preferably Q is CH or C (when substituted by an R^1 group).

Preferably V is O.

Preferably L is $-CH_2-$.

Preferably J is $-CH=CH-$, $-(CH_2)_2-$ or a group $-CHR^7-CH_2-$ where R^7 is as defined above.

Within the definition of formula (Ia):

When m is other than 0, preferred R^1 groups include halogen (particularly fluoro or chloro) or a C_{1-6}alkyl group (particularly methyl). When m is 2 or 3 the groups R^1 can be the same or different. Most preferably m is 1 and R^1 is a methyl group with an ortho relationship with respect to the urea moiety.

When n is other than 0, preferred R^2 groups include halogen (particularly fluoro or chloro), C_{1-6}alkyl group (particularly methyl) or a C_{1-6}alkoxy group (particularly methoxy). When n is 2 or 3 the groups R^1 can be the same or different. Most preferably n is 0 or n is 1 with R^2 being a methoxy group with an ortho relationship with respect to the urea moiety.

When p is other than 0, preferred R^3 groups include halogen (particularly fluoro or chloro) or a C_{1-6}alkyl group (particularly methyl). When p is 2 or 3 the groups R^3 can be the same or different.

R^4 is preferably hydrogen.

Preferred L and J groups include those given above.

Particularly preferred compounds of this invention include

3-(4-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl)-2*H*-pyridin-1-ylmethyl} phenyl)propionic acid,

3-(3-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl)-2*H*-pyridin-1-ylmethyl} phenyl)propionic acid or

(±)-3-(3-{2-Oxo-3-[4-(3-o-tolyl-ureido)phenyl]piperidin-1-ylmethyl} phenyl)propionic acid

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

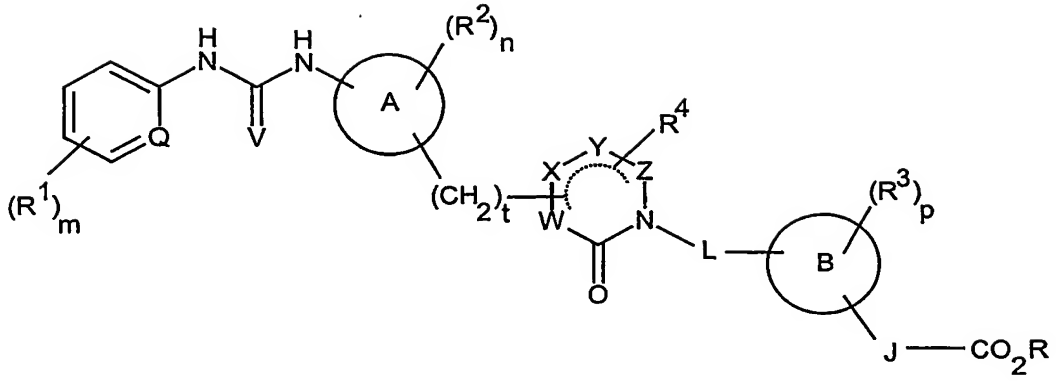
The present invention includes within its scope prodrugs of the compounds of formula (I). Such pro-drugs will be functional derivatives of the compounds of this invention which are readily converted *in vivo* into the claimed compounds.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

It will be appreciated that certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. It will be further appreciated that when J is a group of formula (i) both cis and trans may be formed. The invention also extends to any tautomeric forms and mixtures thereof.

Where used herein the term "pharmaceutically acceptable salt thereof" is used to denote non-toxic salts that are suitable for use in therapy. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19. Pharmaceutically acceptable salts include a salt with an inorganic base, an organic base or a basic amino acid (e.g., an alkali metal salt such as a sodium salt and a potassium salt; an alkali earth metal salt such as magnesium salt and calcium salt; or a salt with an amine such as an ammonium salt, triethylammonium salt, a salt with lysine and the like).

In a further aspect, the present invention also provides for a process for the preparation of a compound of formula (I) which comprises hydrolysis of a carboxylic acid ester derivative of formula (II):



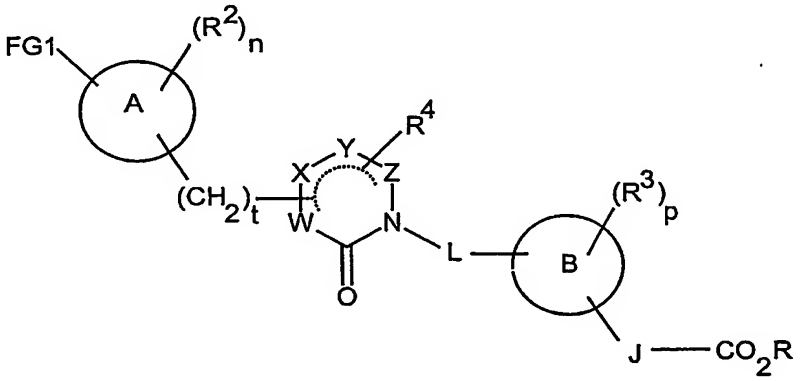
(II)

in which R^1 - R^4, m, n, p, t, A, B, L, J, Q, W, X, Y and Z are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable salt or solvate thereof.

An example of a suitable R group is C_{1-6}alkyl such as methyl or t-butyl. Hydrolysis may either occur via an acidic or an alkaline medium. Such methods are familiar to those skilled in the art.

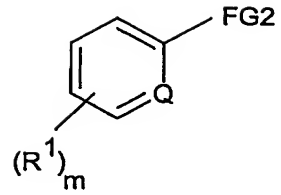
The compounds of formula (II) can be prepared by either:

(a) reacting the compounds of formula (III)



(III)

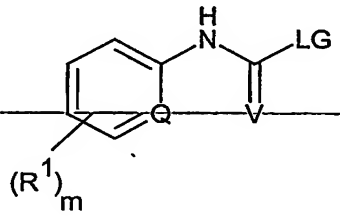
in which R^2 - R^4, n, p, t, A, B, L, J, R, W, X, Y and Z are as defined in formulae (I) or (II) with a compound of formula (IV)



(IV)

in which R^1, m and Q are as defined above and FG1 and FG2 contain appropriate functional groups which are capable of reacting together to form the urea moiety; or

(b) reacting the compound of formula (III) in which FG1 is NH_2 as defined above with the compound of formula (V)



(V)

in which R^1 and m are as defined for formula (I), Q and V combine to form a 5 or 6 membered heterocyclic ring and LG is a leaving group.

For process (a), suitable examples of appropriate FG1 and FG2 groups include:

(i) FG1 is -N=C=O and FG2 is NH_2; or FG1 is NH_2 and FG2 is N=C=O; or

(ii) FG1 is NH_2 and FG2 is NH_2 together with an appropriate urea forming agent.

In process (i) the reaction is typically carried out in an inert solvent such as dichloromethane or acetonitrile at ambient temperature.

In process (ii) the reaction is typically carried out in the presence of an appropriate urea forming agent, such as carbonyl diimidazole or phosgene, a suitable solvent being an inert organic solvent such as dimethylformamide, tetrahydrofuran, or dichloromethane at ambient or elevated temperature optionally in the presence of a base such as triethylamine or pyridine.

For process (b), a suitable example of a leaving group is halogen, particularly chloro. Examples of such reactions include those described by Jung et al. (J. Med. Chem., 1991, 34(3), 1110 and Passerini (J. Chem. Soc., 1954, 2256).

Intermediate compounds of formulae (III), (IV) and (V) are either commercially available or can be prepared using methods described herein, by methods known to those skilled in the art or by analogous methods thereto.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used such as those described in T.W. Greene "Protective Groups in Organic Synthesis".

Compounds of this invention may be tested for *in vitro* biological activity in accordance with the following assay.

Jurkat J6 Scintillation Proximity Assay (SPA)

The Jurkat J6 Scintillation Proximity Assay was used to investigate the interaction of the integrin VLA-4 (Very Late Antigen-4; $\alpha 4\beta 1$; CD49d, CD29) expressed on the Jurkat J6 cell membrane with test compounds. J6 cells (1 million cells/well) were allowed to coat wheat germ agglutinin coated SPA beads (Amersham, 1mg/well) in assay buffer containing 50mM HEPES, 100mM NaCl and 1mM $MnCl_2$ (pH with 4M NaOH to 7.5). Tritiated ^3H Standard Compound A (1-3 nM final assay concentration) and test compounds are dissolved in an appropriate solvent and diluted in assay buffer. Compounds are assayed in singlicate, a four parameter curve fit of Equation 1 being applied. The equilibrium dissociation constant for each compound was calculated according to the method of Cheng & Prusoff. Data is presented as the mean pKi.

Standard compound A is (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy)acetyl]amino}pentanoyl)amino] propanoic acid potassium salt which is described in patent application WO 00/37444 (Glaxo Group Ltd. et al). Tritiated ^3H derivatives may be prepared employing conventional methods.

Equation 1

$$y = \frac{a - d}{1+(\frac{x}{c})^b} + d$$

Where a is the minimum, b is the Hill slope, c is the IC_{50} and d is the maximum. (Maximum and minimum values are those compared to adhesion in the absence of compound and in the presence of the dipotassium salt of 2mM EDTA; Sigma Chemicals, UK, Product No. ED2P). Data is presented as the mean pIC_{50}.

All examples prepared in accordance with this invention were tested in accordance with this procedure and were found to have a pKi > 6.5.

Compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof inhibit α_4 integrin mediated cell adhesion and are believed to be of potential use in the treatment or prophylaxis of such conditions as rheumatoid arthritis (RA); asthma; allergic conditions such as rhinitis; adult respiratory distress syndrome; AIDS-dementia; Alzheimer's disease; cardiovascular diseases; thrombosis or harmful platelet aggregation; reocclusion following thrombolysis; reperfusion injury; skin inflammatory diseases such as psoriasis, eczema, contact dermatitis and atopic dermatitis; diabetes (e.g., insulin-dependent diabetes mellitus, autoimmune diabetes); multiple sclerosis; systemic lupus erythematosus (SLE); inflammatory bowel disease such as ulcerative colitis, Crohn's disease (regional enteritis) and pouchitis (for example, resulting after proctocolectomy and ileoanal anastomosis); diseases associated with leukocyte infiltration to the gastrointestinal tract such as Celiac disease, nontropical Sprue, enteropathy associated with seronegative arthropathies, lymphocytic or collagenous colitis, and eosinophilic gastroenteritis; diseases associated with leukocyte infiltration to other epithelial lined tissues, such as skin, urinary tract, respiratory airway, and joint synovium; pancreatitis; mastitis (mammary gland); hepatitis; cholecystitis; cholangitis or pericholangitis (bile duct and surrounding tissue of the liver); bronchitis; sinusitis; inflammatory diseases of the lung which result in interstitial fibrosis, such as hypersensitivity pneumonitis; collagen disease (in SLE and RA); sarcoidosis; osteoporosis; osteoarthritis; atherosclerosis; neoplastic diseases including metastasis of neoplastic or cancerous growth; wound (wound healing enhancement); certain eye diseases such as retinal detachment, allergic

conjunctivitis and autoimmune uveitis; Sjogren's syndrome; rejection (chronic and acute) after organ transplantation; host vs. graft or graft vs. host diseases; intimal hyperplasia; arteriosclerosis (including graft arteriosclerosis after transplantation); reinfarction or restenosis after surgery such as percutaneous transluminal coronary angioplasty (PTCA) and percutaneous transluminal artery recanalization; nephritis; tumor angiogenesis; malignant tumor; multiple myeloma and myeloma-induced bone resorption; sepsis; and central nervous system injury such as stroke, traumatic brain injury and spinal cord injury.

The compounds of the present invention can be preferably used for the treatment or prevention of asthma, allergic conditions such as rhinitis, inflammatory bowel disease such as ulcerative colitis and Crohn's disease, rheumatoid arthritis, atopic dermatitis, multiple sclerosis and rejection after organ transplantation.

The present invention further provides for a method for the treatment or prophylaxis of conditions in which an inhibitor of α_4 mediated cell adhesion is beneficial which comprises administering to a patient in need thereof a safe and effective amount of a compound of formula (I).

According to the method, an inhibitor can be administered to an individual (e.g., a human) alone or in conjunction with another pharmacologically active agent such as an additional steroidal or non-steroidal anti-inflammatory compound.

The present invention also provides for a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, particularly the treatment of the aforementioned disorders.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of conditions in which an inhibitor of α_4 mediated cell adhesion is beneficial, particularly the aforementioned disorders.

While it is possible for the compounds of the present invention to be administered alone, it is preferable to formulate into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus the invention also provides for a pharmaceutical composition which comprises a therapeutically effective amount of a compound of formula (I) in admixture with a pharmaceutically acceptable carrier or diluent.

The carrier or diluent must be acceptable in the sense of being not deleterious to the recipient thereof. The pharmaceutically acceptable carrier or diluent may be, for example, binders (e.g., syrup, gum arabic, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone), excipients (e.g., lactose, sucrose, corn starch, potassium phosphate, sorbitol, glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol, silica) disintegrators (e.g., potato starch), wetting agents (e.g., sodium laurylsulfate), and the like.

The pharmaceutical compositions include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), intra-articular, topical, nasal inhalation (e.g., with an aerosol) or buccal administration. These formulations are understood to include long-acting formulations known in the art of pharmacy. Oral and parenteral administrations are preferred modes of administration.

The pharmaceutical composition may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired form.

Compositions of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the compounds of the present invention, in the form of a powder or granules, or in the form of a solution or suspension in an aqueous liquid. Formulations for other uses could involve a non-aqueous liquid; in the form of an oil-in-water emulsion or a water-in-oil emulsion; in the form of an aerosol; or in the form of a cream or ointment or impregnated into a transdermal patch for use in administering the compounds of the present invention transdermally, to a patient in need thereof. The compounds of the present invention may also be administered to a patient in need thereof in the form of a bolus, electuary, or paste.

The compounds of the present invention can be administered to a patient in need thereof in amounts sufficient to inhibit α_4 integrin mediated cell adhesion. In another aspect, the compounds of the present invention can be administered to the patient in amounts sufficient to achieve the desired therapeutic and/or prophylactic effect.

The amount of the compounds of formula (I) required to achieve a therapeutic effect will vary with the particular compound, the route of administration, the age, sex, weight, and condition of the subject to be treated, and the particular disorder or disease to be treated. A suitable daily dose of the compound of formula (I), or a pharmaceutically acceptable salt thereof, for a mammalian subject suffering from, or likely to suffer from, any condition as described herein is from 0.1 to 100 mg per kilogram body weight of the mammalian subject, preferably 0.3 to 30 mg/kg of mammal body weight. In the case of parenteral administration, the dose may be in the range of 0.1 to 10 mg of the compound per kilogram body weight, preferably 0.3 to 3 mg/kg of mammal body weight. In the case of oral dosing, a suitable (daily) dose may be in the range of 1 to 100 mg of the compound per kilogram body weight, but preferably 1 to 30 mg of the compound per kilogram, the most preferred dosage being 1 to 10 mg/kg of mammal body weight.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

3-(4-Nitrophenyl)pyridine (D1)

1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.2 g, 0.2 mmol) was added to a stirred and degassed solution of 4-bromonitrobenzene (5 g, 24.8 mmol) and pyridine-3-boronic acid (3.4 g, 27.2 mmol) in dimethyl formamide (50 mL) and 2N sodium carbonate solution in water (20 mL). The reaction mixture was stirred at 100°C for 18 hours, then allowed to cool. The solution was filtered through celite, then ethyl acetate (200 mL) was added and the organic phase was washed three time with brine (200 mL). The organic was dried (anhydrous magnesium sulfate), concentrated and purified by chromatography on silica gel (30% v/v ethyl acetate in petroleum ether) to afford the title compound as a solid.

Description 2

3-(4-Nitrophenyl)pyridine-1-oxide (D2)

m-Chloroperbenzoic acid (6.9 g, 40.0 mmol) was slowly added to a solution of 3-(4-nitrophenyl)pyridine (4 g, 20.0 mmol) in tetrahydrofuran (200 mL) and the reaction mixture was stirred at room temperature for 1 hour. The solution was poured into aqueous sodium thiosulfate and the resultant mixture was concentrated. Trituration with ethyl acetate afforded the title compound as a solid.

Description 3

3-(4-Nitrophenyl)-1H-pyridin-2-one (D3)

3-(4-Nitrophenyl)pyridine-1-oxide (2.5 g, 11.6 mmol) was stirred at reflux in acetic anhydride (25 mL) for 18 hours, then allowed to cool. The reaction mixture was concentrated and concentrated hydrochloric acid (25 mL) was added. The solution was stirred at reflux for 4 hours, then allowed to cool. The reaction mixture was poured onto ice/water and filtration followed by drying under high vacuum afforded the title compound as a solid.

Description 4

3-(4-Hydroxymethylphenyl)acrylic acid ethyl ester (D4)

4-Bromobenzyl alcohol (10.5 g, 56.1 mmol), triphenylphosphine (0.5 g, 1.9 mmol) and palladium acetate (0.5 g, 2.2 mmol) were stirred at reflux in ethyl acrylate (20 mL) and triethylamine (100 mL) for 72 hours, then allowed to cool. The reaction mixture was filtered through celite, then concentrated. The crude solid was purified by chromatography on silica gel (20% v/v ethyl acetate in petroleum ether) to afford the title compound as an oil.

Description 5

3-(4-Hydroxymethylphenyl)propionic acid ethyl ester (D5)

3-(4-Hydroxymethylphenyl)acrylic acid ethyl ester (3 g, 14.5 mmol) and palladium on charcoal (0.3 g) in ethanol (30 mL) was stirred for 4 hours under atmospheric pressure of hydrogen. The reaction mixture was filtered through celite and concentrated to afford the title compound as an oil.

Description 6

3-(4-Chloromethylphenyl)propionic acid ethyl ester (D6)

To a stirred solution of 3-(4-hydroxymethylphenyl)propionic acid ethyl ester (2.9 g, 13.9 mmol) in triethylamine (4.0 mL, 27.8 mmol) and dichloromethane (30 mL) was slowly added at 0°C mesyl chloride (1.6 mL, 20.9 mmol). The solution was stirred at room temperature for 18 hours, then the solution was washed with 1N aqueous hydrochloric acid. The organic phase was dried (anhydrous magnesium sulfate) and concentrated to afford the title compound as an oil.

Description 7

3-{4-[3-(4-Nitrophenyl)-2-oxo-2H-pyridin-1-ylmethyl]phenyl}propionic acid ethyl ester (D7)

3-(4-Nitrophenyl)-1H-pyridin-2-one (200 mg, 0.93 mmol), 3-(4-chloromethyl-phenyl)propionic acid ethyl ester (270 mg, 1.20 mmol) and cesium carbonate (900 mg, 2.78 mmol) were stirred for 18 hours in dimethyl formamide (5 mL) at room temperature. The reaction mixture was filtered through celite, concentrated and the crude mixture was purified by chromatography on silica gel (50% v/v ethyl acetate in petroleum ether) to afford the title compound as a solid.

Description 8

3-{4-[3-(4-Aminophenyl)-2-oxo-2H-pyridin-1-ylmethyl]phenyl}propionic acid ethyl ester (D8)

3-{4-[3-(4-Nitrophenyl)-2-oxo-2H-pyridin-1-ylmethyl]phenyl}propionic acid ethyl ester (300 mg, 0.74 mmol) and palladium on charcoal (30 mg) were stirred at room temperature in ethanol (10 mL) under atmospheric pressure of hydrogen for 3 hours, then the reaction mixture was filtered through celite and concentrated. The crude oil was purified by chromatography on silica gel (50% v/v ethyl acetate in petroleum ether) to afford the title compound as an oil.

Description 9

3-(4-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl)-2H-pyridin-1-ylmethyl}phenyl)propionic acid ethyl ester (D9)

3-{4-[3-(4-Aminophenyl)-2-oxo-2H-pyridin-1-ylmethyl]phenyl}propionic acid ethyl ester (60 mg, 0.16 mmol) and o-tolyl isocyanate (40 μL, 0.32 mmol) were stirred at room temperature in dichloromethane (5 mL) for 3 hours, then the reaction mixture was concentrated. Trituration with diethyl ether afforded the title compound as a solid.

Description 10

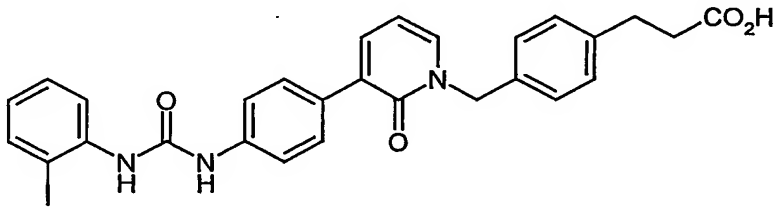
(±)-3-(3-{2-Oxo-3-[4-(3-o-tolyl-ureido)phenyl]piperidin-1-ylmethyl}phenyl)propionic acid ethyl ester (D10)

(E)-3-{3-[3-(4-Nitrophenyl-2-oxo-2*H*-pyridin-1-ylmethyl]phenyl}acrylic acid ethyl ester (85 mg, 0.21 mmol) with 10% palladium on charcoal in ethanol (20 mL) was hydrogenated at atmospheric pressure for 18 hours. The reaction mixture was then filtered through celite, evaporated to dryness and purified by chromatography on silica gel with 70% ethyl acetate/petroleum ether to give the title compound as an oil.

MS (AP+ve): $[M+H]^+$ at m/z 381 ($C_{23}H_{28}N_2O_3$ requires $[M+H]^+$ at m/z 381).

Example 1

3-(4-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl]-2*H*-pyridin-1-ylmethyl}phenyl)propionic acid (E1)



3-(4-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl)-2H-pyridin-1-ylmethyl}phenyl)propionic acid ethyl ester (55 mg, 0.11 mmol) and lithium hydroxide (50 mg, 2.5 mmol) were stirred at 60°C for 30 minutes in tetrahydrofuran (5 mL) and water (5 mL). The reaction mixture was acidified to pH 1 with 1N aqueous hydochloric acid and extracted with ethyl acetate. The organic layer was dried (anhydrous magnesium sulfate) and evaporated to dryness to afford the title compound as a solid.

^{1}H NMR δ (DMSO-d6): 2.21-2.27 (5H, m), 2.73-2.80 (2H, t), 5.12 (2H, s), 6.28-6.34 (1H, t), 6.89-6.95 (1H, m), 7.12-7.25 (6H, m), 7.51-7.63 (5H, m), 7.68-7.77 (2H, m), 9.28 (1H, s), 10.47 (1H, s).

MS (ACPI-ve): $[M]^-$ at m/z 481, $[M-H]^-$ at m/z 480 ($C_{29}H_{27}N_3O_4$ requires $[M-H]^-$ at m/z 480).

Example 2

3-(3-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl]-2*H*-pyridin-1-ylmethyl}phenyl)propionic acid (E2)

The title compound was prepared using an analogous procedure to that of Example 1.

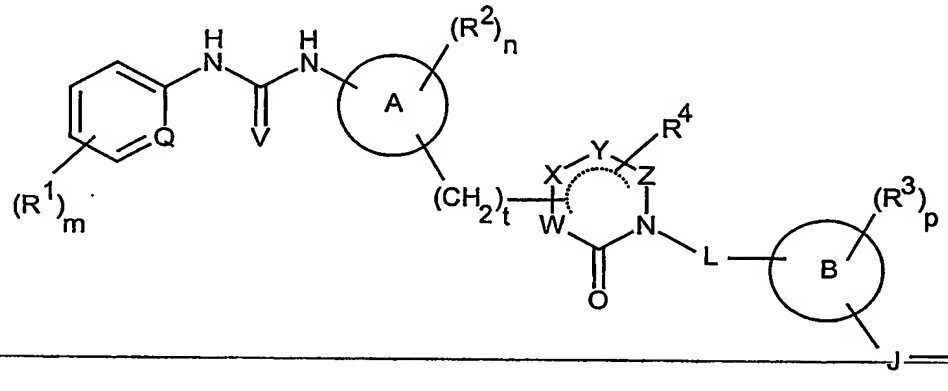
Example 3

(±)-3-(3-{2-Oxo-3-[4-(3-o-tolyl-ureido)phenyl]piperidin-1-ylmethyl}phenyl)propionic acid

The title compound was prepared in a similar manner to Example 1 except that the hydrogenation step was carried out under modified conditions as detailed in Description 10.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(I)

wherein

A and B are independently aryl or heteroaryl;

Q is C, CH or together with the group V forms a 5 or 6 membered heterocyclic ring;

R^1, R^2 and R^3 are independently C_{1-6}alkyl, halogen, C_{1-6}alkoxy, hydroxy, cyano, CF_3, nitro, C_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino, carboxy, C_{1-6}alkanoyl, amido, mono or di-C_{1-6}alkyl amido, $NHCOR^9$ or $NHSO_2R^9$ in which R^9 is C_{1-6}alkyl, C_{3-7}cycloalkyl or phenyl optionally substituted by up to three groups selected from C_{1-6}alkyl, halogen, C_{1-6}alkoxy, cyano, phenyl or CF_3;

R^4 is hydrogen, C_{1-6}alkyl, halogen or C_{1-6}alkoxy;

V is O, S, NH, N-C_{1-6}alkyl, NNO_2 or NCN or V together with the group Q forms a 5 or 6 membered heterocyclic ring;

W, X, Y and Z are independently C, CH or CH_2;

------ represents a single or double bond;

L is $-(CH_2)_q-$ where q is 0, 1, 2 or 3;

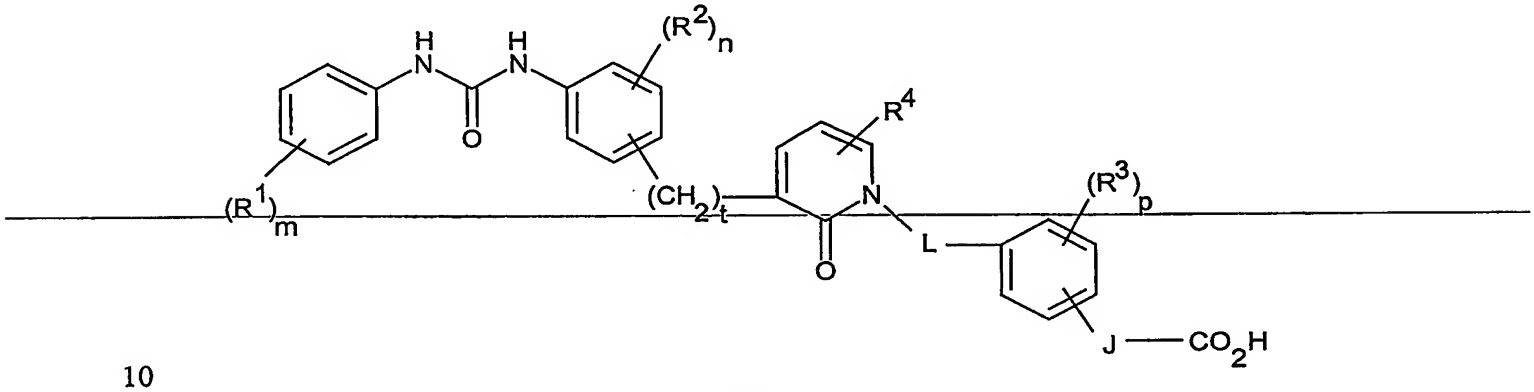
J is (i) a group $-CR^5 = CR^6-$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl; or

(ii) a group -CHR^7-CHR^8- where R^7 and R^8 are independently hydrogen, C_{1-6}alkyl or is a group NHCOR^9 or NHSO$_2$R^9 in which R^9 is as defined above;

m, n and p are independently 0, 1, 2 or 3;

t is 0, 1 or 2.

2. A compound according to claim 1, wherein the compound is of formula (Ia):



(Ia)

wherein:

R^1, R^2, R^3, R^4, L, J, m, n, p and t are as defined in formula (I).

3. A compound according to claim 1 or 2, in which L is -CH$_2$-.

4. A compound according to claim any of the preceding claims in which J is -CH = CH-, -(CH$_2$)$_2$- or a group -CHR^7-CH$_2$- where R^7 is as defined in claim 1.

5. A compound according to claim 1 which is:

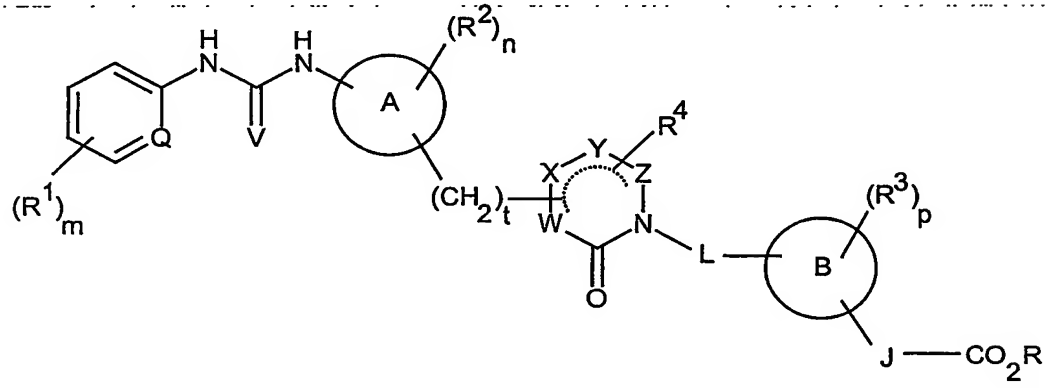
3-(4-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl]-2*H*-pyridin-1-ylmethyl} phenyl)propionic acid,

3-(3-{2-Oxo-3-[4-(3-*o*-tolyl-ureido)phenyl]-2*H*-pyridin-1-ylmethyl} phenyl)propionic acid or

(±)-3-(3-{2-Oxo-3-[4-(3-o-tolyl-ureido]phenyl]piperidin-1-ylmethyl} phenyl)propionic acid

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

6. A process for the preparation of a compound of formula (I) which comprises hydrolysis of a carboxylic acid ester derivative of formula (II):



(II)

in which R^1 - R^4, m, n, p, t, A, B, L, J, Q, W, X, Y and Z are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable salt or solvate thereof.

7. A pharmaceutical composition which comprises a therapeutically effective amount of a compound according any one of claims 1 to 5 in admixture with a pharmaceutically acceptable carrier or diluent.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 - 5 or a pharmaceutically acceptable salt, solvate or prodrug thereof together with another therapeutically active agent.

9. A compound according to any one of claims 1 to 5 for use in therapy.

10. The use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment of conditions in which an inhibitor of α_4 mediated cell adhesion is beneficial.

11. A method for the treatment or prophylaxis of conditions in which an inhibitor of α_4 mediated cell adhesion is beneficial which comprises administering to a patient in need thereof a safe and effective amount of a compound according to any one of claims 1 to 5.

12. The method according to claims 11, wherein said condition is selected from the group consisting of rheumatoid arthritis; asthma; allergic conditions; adult respiratory distress syndrome; AIDS-dementia; Alzheimer's disease; cardiovascular diseases; thrombosis or harmful platelet aggregation; reocclusion following thrombolysis; reperfusion injury; skin inflammatory diseases; diabetes; multiple sclerosis; systemic lupus erythematosus; inflammatory bowel disease; diseases associated with leukocyte infiltration to the gastrointestinal tract; diseases associated with leukocyte infiltration to epithelial lined tissues; pancreatitis; mastitis; hepatitis; cholecystitis; cholangitis or pericholangitis; bronchitis; sinusitis; inflammatory diseases of the lung; collagen disease; sarcoidosis; osteoporosis; osteoarthritis; atherosclerosis; neoplastic diseases; wound; eye diseases; Sjogren's syndrome; rejection after organ transplantation; host vs. graft or graft vs. host diseases; intimal hyperplasia; arteriosclerosis; reinfarction or restenosis after surgery; nephritis; tumor angiogenesis; malignant tumor; multiple myeloma and myeloma-induced bone resorption; sepsis and central nervous system injury.

13. The method according to claim 11, wherein said condition is asthma, allergic conditions, inflammatory bowel disease, rheumatoid arthritis, atopic dermatitis, multiple sclerosis or rejection after organ transplantation.

ABSTRACT

The present invention relates to novel compounds, processes for their preparation, compositions comprising them and their use in the treatment of diseases capable of being modulated by the inhibition of cell adhesion.